REMARKS

Claims 1-6 and 9-11 are pending in this application.

Rejections under 35 U.S.C. § 103

Claims 1-6 and 9-11 were rejected under 35 U.S.C. 103(a) as allegedly being "unpatentable over the combination of Cooke et al. (U.S. Pat. No. 4,725,549) and A.M. Walker (TEM, 5(5):195-200) in view of Maciejewski et al. (J. Biol. Chem. 270(17): 27661-27665, 1995, for the reasons of record in paper #13, 16, 25 and 30."

Cooke et al. was cited by the Examiner for its teaching of recombinant prolactin. Walker was cited by the Examiner "for the teaching that a serine in prolactin within the region of amino acids 170-180 is highly conserved between species and is a major site of phosphorylation." Maciejewski et al. was cited by the Examiner "only for the teaching that substitution of serine mimics phosphorylation." The Examiner has concluded that in view of the combination of the cited references "suggestion is in the art" for "modifying other prolactin molecules in a similar manner, i.e. by substitution of the major phosphorylated serine residue, in order to mimic the phosphorylation."

Applicant disagrees and respectfully traverses the rejection. Maciejewski et al. would not suggest to one of ordinary skill in the art that "substitution of serine mimics phosphorylation" since two of the three substitutions discussed by Maciejewski et al. did not mimic phosphorylation. Thus, there is no motivation to combine Maciejewski et al. and Walker, nor, in particular, would one of skill in the art expect that substitution of human prolactin at residue 179 would mimic phosphorylated prolactin. Moreover, even if combined, the cited references fail to provide all elements of the claimed invention.

The Maciejewski Reference

The Examiner noted on page 3 of the Office Action that Applicant's arguments were not persuasive in opposing the suggestion that Maciejewski et al. could be cited to suggest "that substitution of the major phosphorylation site in bovine prolactin mimicked the effects of phosphorylation." In support of this position, the Examiner relies on the title of Maciejewski et al. which reads "Mutation of Serine 90 to Glutamic Acid Mimics Phosphorylation of Bovine Prolactin" and notes that the journal in which the article was published was "a peer-reviewed journal" (page 3, lines 7-10). Applicant notes that Maciejewski et al. discusses the substitution of serine 90, which is claimed to mimic phosphorylation of serine 90 of bovine prolactin. Maciejewski et al. states that it is their aim to "elucidate the roles of individual phosphorylation sites." (see page 27662, second paragraph, emphasis added) and makes no claim that their results are generally applicable to other serine residues in prolactin of any species. In fact, Maciejewski et al. found that mutation of two other serine residues did not mimic the biological activity of the phosphorylated protein (page 27664, second column, fourth full paragraph). Further, Maciejewski et al. teach that it is the specific structural features around serine 90 that account for their results (see discussion generally). Thus, a fair reading of Maciejewski et al., without the

benefit of hindsight colored by the instant application, shows that Maciejewski et al. teach away from a conclusion that their results are applicable to other distinct serine residues.

Maciejewski et al. does not teach substitution of position 179: the Examiner notes that "Maciejewski et al. was not cited for a teaching of substitution of position 179 in human prolactin" (page 4, line 4). Instead, the Examiner cites Walker as providing "that a serine in prolactin within the region of amino acids 170-180 is highly conserved between species and is a major site of phosphorylation and is critical for biological activity" (page 4). However, Walker does not suggest substitution of position 179, nor does Walker suggest that substitution at position 179 would mimic phosphorylation.

In fact, the present invention provided surprising and unexpected results. At the time the invention was made, one of skill in the art would not have expected that substituting glutamic acid at position 179 would result in mimicry of the phosphorylation as found with substitution of glutamic acid at position 90 of bovine prolactin. As discussed by Dr. Walker in her Declaration, and as discussed in the accompanying Declaration by Dr. Charles Clevenger of the University of Pennsylvania, the structure of prolactin near residue 90 was known at the time to be very different than the structure near residue 179.

Applicant respectfully notes that the Examiner has not provided any teaching or suggestion that substitution of the major phosphorylation site in prolactin of another species, i.e. human prolactin, would also lead to a mimic of phosphorylated prolactin. Neither Maciejewski et al. nor Walker suggests substitution of position 179; neither Maciejewski et al. nor Walker suggests that substitution at position 179 would mimic phosphorylation. The Examiner, and not Maciejewski et al., has suggested that based on the findings with respect to substitution of serine 90, "one of ordinary skill in the art would also expect that substitution of this position with glutamic acid would result in mimicry of the phosphorylation as found in the bovine prolactin." Accordingly, and as discussed in greater detail below, Applicant respectfully submits that one of skill in the art at the time would not have expected that substitution at residue 179 of human prolactin would behave like, or would be expected to behave like, substitution at residue 90 of bovine prolactin.

Thus Walker and Maciejewski et al., either alone or taken together, fail to provide at least these elements of the present invention. For this reason alone, Applicant respectfully submits that the rejection of claims 1-6 and 9-11 under 35 U.S.C. § 103(a) is overcome.

The Walker Declaration

In order to support a rejection of claims 1-6 and 9-11 under 35 U.S.C. §103(a), it must be shown that the invention would be obvious to one of ordinary skill in the art in view of the cited references, and that one of ordinary skill in the art would have had a reasonable expectation that practice of the invention would be successful. The Examiner considered the Walker Declaration filed on October 26 2002 to be "ineffective to overcome the Maciejewski et al. reference." However, the Examiner does not comment on Walker's statement in the Declaration that "one of skill in the art would not expect substitution of serine residues 177 or 179 in human or bovine prolactin with glutamic acid to produce a mimic of naturally phosphorylated prolactin." Lacking

any expectation that substitution of serine residues 177 or 179 would mimic phosphorylation of native prolactin, the invention itself is not obvious, nor would one of ordinary skill in the art have a reasonable expectation of success. Accordingly, Applicant respectfully submits that the Walker Declaration demonstrates that claims 1-6 and 9-11 are not obvious over the cited references.

The Expert Declaration

Applicant submits a Declaration under 37 C.F.R. § 1.132 in support of the application. This Declaration has been provided by Dr. Charles Clevinger, M.D., Ph.D., an expert in the field of prolactin and other hormones. As is evident from his *curriculum vitae* (enclosed), Dr. Clevenger has performed research and published extensively in the fields of prolactin, prolactin receptors, hormones and hormone action in general. Dr. Clevenger is Co-Director of the Residency Program in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine in Philadelphia, Pennsylvania. He has published over 40 articles in peer-reviewed journals, and has published an additional 17 reviews, book chapters, and editorials. He has given numerous invited lectures, chaired sessions at meetings, and is presently Principal Investigator of three grants dealing with prolactin and prolactin receptors.

As reiterated by the Examiner on page 4, the "instant rejection is one of obviousness." In order to support a rejection of claims 1-6 and 9-11 under 35 U.S.C. §103(a), it must be shown that the invention would be obvious to one of ordinary skill in the art in view of the cited references, and that one of ordinary skill in the art would have had a reasonable expectation that practice of the invention would be successful. As discussed by Dr. Clevenger, one of skill in the art would not have expected that substitution of serine residue 179 in human or bovine prolactin with glutamic acid would produce a mimic of naturally phosphorylated prolactin. See, for example, Dr. Clevenger's paragraph 6-10. Dr. Clevenger notes that Maciejewski et al. "report that replacement of serine residues 26 and 34 with glutamic acid does not affect biological activity" (9-10 of paragraph 7), thus removing any basis for a reasonable expectation that such substitution at a different residue in prolactin from a different species would necessarily affect biological activity. Dr. Clevenger further notes that "the location of the serine 90 in bovine prolactin may have been anticipated to reside in a flexible peptide loop between two alpha helices" (lines 3-4 of paragraph 8). In contrast, Dr. Clevenger notes that "the serine 179 residue in human prolactin may have been anticipated to be buried in the hydrophobic alpha helical core of human prolactin" (lines 5-6 of paragraph 8) and concludes that "any one of 'ordinary skill' would anticipate that mutations at these sites would have significantly different effects" (lines 8-9 of paragraph 8). Accordingly, Dr. Clevenger declares that "these references do not make obvious that substitution of amino acid residue 179 of human prolactin would result in a variant that mimics phosphorylated prolactin" (lines 2-4 of paragraph 6 of the Declaration).

In the Declaration, Dr. Clevenger states that the cited references Maciejewski, Walker and Cooke would not have enabled one of ordinary skill in the art at the time to predict using established scientific rationale the effects of amino acid substitution at residue 179 of bovine prolactin or of prolactin of other species based on known structural and functional differences between residues 90 and 179. Thus, at the time the invention was made, one of skill in the art

would not expect that the results of experiments suggesting that substitution of serine 90 might mimic phosphorylated prolactin to be applicable to other distinct and distant serine residues in prolactin. Further, Dr. Clevenger specifically states that "one of ordinary skill in the art at the time of the invention would not have expected that substitution of serine residue 179 with glutamic acid would produce a mimic of naturally phosphorylated prolactin that would be capable of super-antagonizing the growth-promoting effects of non-phosphorylated prolactin" (lines 7-10 of paragraph 11).

Lacking any expectation that substitution of serine residues 177 or 179 would mimic phosphorylation of native prolactin, the invention itself is not obvious, nor would one of ordinary skill in the art have a reasonable expectation of the success of such a substitution in mimicking phosphorylation of human prolactin. Dr. Clevinger states (paragraph 9 of the Declaration): "Thus, it is my considered scientific opinion that, based on the disclosures of Cooke et al., the Walker 1994 article, and the Maciejewski et al. paper, one could not predict the biological effects of an experimental mutation in bovine prolactin...." Accordingly, Applicant respectfully submits that the Clevenger Declaration demonstrates that claims 1-6 and 9-11 are not obvious over the cited references.

As stated by an expert in the field, Applicant points out that at the time the invention was made, one skilled in the art would not have concluded that Maciejewski taught that substitution of the most phosphorylated serine would mimic phosphorylated prolactin. As a result, one of skill in the art would not have been motivated to combine the cited references, as the Examiner did in making the present rejection. Further, the declaration provides evidence and sound scientific reasoning in support of the notion that, without impermissible hindsight reasoning, the cited combination of references would not establish a reasonable expectation of success for the production of a mimic of phosphorylated prolactin by substituting residues 177 or 179 which are distinct from residue 90 in human or bovine prolactin. In light of the evidence of the Clevenger Declaration and of these arguments, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

Impermissible Hindsight

The Examiner suggests that hindsight is permissible, stating "it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning" (page 5) citing *In re McLaughlin* to say that "such reconstruction is proper" if it "does not include knowledge gleaned only from the applicant's disclosure." Applicants respectfully note that the Examiner's reconstruction does include knowledge gleaned only from the present disclosure; for example, no cited reference discloses mutation or substitution of serine 179 in human prolactin, nor does any cited reference disclose that such mutation or substitution mimics phosphorylation of native human prolactin. Thus, without the knowledge gleaned from the Applicant's disclosure, it is clear that the instant invention is not obvious over the prior art.

In addition, Applicant respectfully submits that hindsight is never proper. One cannot properly take an applicant's disclosure and use it as a guide in an attempt to show obviousness. "Combining prior art references without evidence of such a suggestion, teaching or motivation

simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). Applicants respectfully submit that the Examiner's conclusion of obviousness is improper for being based on impermissible hindsight reasoning. Accordingly, for this reason as well, Applicant submits that the rejection of claims 1-6 and 9-11 under 35 U.S.C. § 103(a) is overcome.

CONCLUSIONS

Applicants respectfully submit that the pending claims are not obvious in view of the cited art, and respectfully request the reconsideration and allowance of claims 1-6 and 9-11.

All claims pending in this application being believed to be in prima facie condition of allowance, an early action to that effect is respectfully solicited. Should the Examiner find that there are any further issues outstanding, she is respectfully invited to contact the undersigned attorney at the telephone number indicated below.

Please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **39754-0611 1CP1CP**.

Respectfully submitted,

Date: June 2, 2003

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